REMARKS

Claims 1, 10, 64 and 65 were pending and under examination in the subject application. By the amendment, Claims 1 and 10 have been canceled without prejudice or disclaimer, Claim 64 has been amended, and new Claim 68 has been added. Applicant maintains that the claim amendments do not raise an issue of new matter. Support for the amendments to the claims can be found at least in the previous version of the claims. Therapeutically effective amounts of selective serotonin re-uptake inhibitors (SSRI) are well known in the art and can be found, for example, in the Physicians' Desk Reference, the manufacturer's product literature, the online Encyclopedia of Medical Disorders, and the online Wikipedia Encyclopedia. Entry of the amendments is respectfully requested.

Summary of October 22, 2009 Interview

Applicant thanks the Examiner for the courtesy of a personal interview that was held at the U.S. Patent Office on October 22, 2009 with the Examiner, applicant and applicant's attorneys. Applicant concurs with the Examiner's Interview Summary in which the Examiner indicated "Applicants' presented data showing the unexpected results with low dose (5-15 mg) pipamperone. Applicants' will consider amending the claims to advance prosecution." Data from the applicant are included in the accompanying Supplemental Information Disclosure Statement (SIDS) and discussed below.

Provisional Obviousness-type Double Patenting Rejection

Applicant acknowledges the provisional rejection of Claims 1 and 10 over Claims 82-84 and 100-101 of later-filed co-pending U.S. Patent Application 10/580,962. Applicant notes that Claims 1 and 10 have herein above been canceled thereby rendering moot this rejection.

Rejections under 35 U.S.C. §112, First Paragraph

Claims 1, 10, 64 and 67 are rejected as not enabled for reciting prodrugs and active metabolites of the specified compounds. The Claims 1 and 10 have herein above been canceled, and Claim 64 has herein above been amended to delete the phrase "or a pro-drug." Applicant respectfully maintains that it would not require undue experimentation for the skilled artisan to practice the claimed invention using an active metabolite of one of the seven compounds specified in Claim 64. The Examiner is also referred to the download from Anxieties.com in the accompanying SIDS. On page 3, under "C. General Anxiety," it is indicated that "[a]ll of the SSRIs appear beneficial..." Reconsideration and withdrawal of this rejection are respectfully requested.

Claims 1, 10, 64 and 67 are also rejected as failing to comply with the written description requirement. Reconsideration and withdrawal of this rejection are respectfully requested in view of the discussion of the present invention set forth below.

Rejections under 35 U.S.C. §103(a)

Claims 1 and 64 are rejected as being unpatentable over Cremers (US 2003/0032636) in view of Prinssen et al. (Eur. J. Pharmacol, 388:57-67, 2000).

Claims 10 and 65 are rejected as being unpatentable over Cremers (US 2003/0032636) in view of Prinssen et al. (Eur. J. Pharmacol, 388:57-67, 2000) and further in view of Bymaster (WO 98/11897).

Claims 1, 10, 64 and 6 are rejected as being unpatentable over Bymaster (WO 98/11897) in view of Prinssen et al. (Eur. J. Pharmacol, 388:57-67, 2000).

Applicant respectively traverses these rejections.

The present invention

Background: The claimed invention requires the administration of pipamperone in an unprecedented low dose of 5 to 15 mg. One of the main problems with contemporaneous psychoactive drugs is their side effects, which limit the usability of these drugs. For instance, the selective serotonin re-uptake inhibitors (SSRIs), which are generally considered to be the first-line antidepressants of choice, block the serotonin transporter responsible for pre-synaptic reuptake. Thus, the availability of synaptic serotonin is augmented, leading to a *stimulation* of various serotonin (5-HT) receptors. However, the simultaneous stimulation of the pre- and postsynaptic serotonin receptors results in several inhibitory effects. The enhanced availability of serotonin stimulates the 5-HT2A receptor which in turn has an inhibitory effect on 5-HT cell bodies via excitation of glutamatergic pathways and 5-HT1A receptor stimulation via specific intracellular biochemical pathways in 5-HT cell bodies. Hence, administration of SSRIs causes a negative feedback, which limits the antidepressant actions of these drugs.

Dose-effect of pipamperone: The inventor surprisingly found that the use of a *daily low dose of 5 - 15 mg* of pipamperone augments the effect of a SSRI in treating a disease or disorder with an underlying dysregulation of the emotional functionality. At the claimed daily low dose, the inventor surprisingly found that pipamperone has a specific, but double effect, *i.e.* a high selective D4 *and* 5-HT2A receptor antagonistic effect. Thus, serotonin, which has enhanced availability due to the action of the SSRI cannot bind to the serotonin 2A receptor. As a corollary, the efficacy of the SSRI is increased, but also the cognitive and behavioural problems induced by enhanced D4 stimulation in the meso-cortical cortex as a result of the augmented availability of dopamine via 5-HT2A antagonism is prevented. As such, pipamperone can exert its augmenting effect on the second, SSRI compound. This effect has not been described in the prior art, nor is there

any hint towards such an effect. This daily low dose of pipamperone has *not* been used in the prior art.

Pipamperone as a sedative neurolepticum: In the prior art, pipamperone is used at higher doses acting as a *sedative neurolepticum* (see e.g. Squelart et al. (1977) as well as the manufacturer's instructions, both of record). As a corollary, the prior art teaches using the highest tolerable dose for treating psychoses. However, at these higher doses pipamperone has no therapeutic effect on the SSRI because an antagonistic activity towards the *D2* and *alpha-adrenergic* receptor takes place, which dominates the clinical effect. This is well-known in the art. This antagonistic activity happens in such a way that negative emerging symptoms like D2 antagonistic related signs such as emotional blunting and cognitive problems (the so-called "neuroleptic induced deficit syndrome") and alpha-adrenergic related signs such as dizziness, decreased blood pressure and drowsiness may counteract the symptoms of, but certainly not treat, and least of all, augment the effect of the SSRI in the treated mood or anxiety disorder.

The present invention does not involve a mere optimization of dosage by routine experimentation. Rather, it is well-known that pipamperone at the ubiquitously used (high) prior art doses indeed decreases the symptom of psychological anxiety (see e.g. "Dipiperon" of record). This effect of pipamperone results from a neuroleptic-sedative effect. Specifically, it is known that the high dose pipamperone results in D2 receptor-related dopaminergic and H1 receptor-related histaminergic antagonism, which is responsible for the neuroleptic-sedative effect. This antagonizing effect (resulting in this neuroleptic-sedative effect) is absent at the claimed low dose of 5-15 mg/day. Accordingly, there would be no incentive to decrease the amount of pipamperone administered, since this would lower the neuroleptic-sedative effect.

Indeed, the prior art teaches away from using a low dose.

For instance, Dipiperon (of record) teaches away from this low dose range. For adults, Dipiperon on page 1 teaches an initial dose of 40 to 80 mg a day, and that if necessary the dose may be increased to a maximum of 360 mg per day. For children the initial dose is 20 mg per day, and the optimal therapeutic dose varies from 20 to 40 mg per day. There is no teaching or suggestion in the cited references to administer pipamperone at a lower dose than the recommended dose. To the contrary, the teaching is always to increase the dose.

In addition, it is noted that the World Health Organization lists a Defined Daily Dose (DDD) for pipamperone of 0.2 g (200 mg) (see download from WHO website in accompanying SIDS).

Applicant also notes the Experimental Examples presented in related U.S. Patent Application Nos. 10/984,683 [US 2005/0203130] and 10/580,962 [US 2007/0078162]. The Examples show the advantages of using pipamperone with citalopram to treat depression (Example 3), obsessive-compulsive disorder (Example 4), and panic disorder (Example 5). Obsessive-compulsive disorder and panic disorder are types of anxiety disorders (see, for example, "Diagnostic and Statistical Manual of Mental Disorders" published by the American Psychiatric Association, which is referred to in paragraph [0058] on page 13 of the present application).

PK/PD modeling of pipamperone and citalopram

In order to establish the *in vivo* receptor occupancy of pipamperone, the inventor conducted PK-PD modeling. By linking the pharmacokinetics and pharmaco-dynamics, a dose-concentration-response relationship was established and evaluated. Subsequently, the effect-time courses resulting from a drug dose were described and predicted. Efficacy of pipamperone, *i.e.* a 5-HT_{2A} receptor antagonistic effect, is expected with a Receptor Occupancy (RO) of $\geq$60% of 5-HT_{2A} at $C_{average}$ (C_{avg}), while adverse effects are expected

with >10% Receptor Occupancy of D2 and H1 receptors at C_{avg}. The modeling indicates:

1. serotonin **5-HT$_{2A}$** receptor: a positive clinical effect, since over >60% RO;
2. dopamine-4 (**D4**) receptor: a positive clinical effect, since over >40% RO;
3. dopamine-2 (**D2**) receptor: absence of a negative effect, since <10% RO; and
4. histamine **H1** receptor: absence of a negative effect, since <10% RO.

Notably, relevant H1-receptor binding (>10% RO) results in sedative effects, while relevant D2-receptor binding (>10% RO) results in a neuroleptic effect and extrapyramidal symptoms (see e.g. Leysen et al. (1998), of record). This neuroleptic sedative effect is not present at the claimed low dose of 5-15 mg pipamperone per day. On the other hand, relevant blockade of the **5-HT$_{2A}$** receptor and the **D4** receptor remains at the claimed low dose of 5-15 mg pipamperone per day. D4 receptor activation results in cognitive and behavioral problems, while 5-HT$_{2A}$ receptor activation results in negative feedback loop on 5-HT$_{1A}$ receptor activation. Thus, the negative effects which are experienced with other drugs are absent. These features are unique to a pipamperone, but only at a **low dose**. These features have never been recognized in the art, and even less their potential in combined medication.

From this study, the following conclusions can be made:

- The optimal dose range is 5 - 15 mg pipamperone per day; and
- The optimal dose is 10 mg pipamperone per day.

Hence the PK/PD modeling results substantiate the observations by the inventor in that low amounts of pipamperone have a relevant clinical effect. The modeling data are presented in the Buntinx et al. 2008 poster and the Buntinx et al. 2008 Abstract attached in the accompanying SIDS. A blow-up of the modeling plot from the poster is attached with the poster. See also Peremans et al. (2008) for data showing that low dose pipamperone blocks serotonin-2A receptors *in vivo* (submitted in accompanying SIDS).

Applicant intends to submit a supplemental report in support of the present

invention after the data is publicly presented on December 9, 2009.

Rejection over cited references

The Examiner asserts that Cremers teaches combinations of SSRIs with 5-HT_{2C} antagonists and that Prinssen teaches that pipamperone is a 5-HT_{2C} antagonist.

It is respectfully noted that for a pharmacological effect to occur, any drug has to be present in sufficient quantities. Determination of sufficient quantities is linked to binding affinities of the drug to its target. Inherently, a drug with low binding affinity for its target needs to be present in higher quantities to achieve the same effect compared to a drug with high binding affinity for its target. In the context of the present invention, the drug is pipamperone, and the target is a receptor involved in dopamine and serotonin signaling. In this respect, reference is made to Leysen et al. (Int J Psychiatry Clin Practice (1998) 2:S3-S17, of record) for a comparison of receptor binding profiles of, among others, pipamperone.

From Table 1 of Leysen it is clear that pipamperone has a different binding affinity (determined as log Ki or pKi) for various receptors:

a) pKi = -6.92 for 5-HT_{2C}

b) pKi = -8.19 for 5-HT_{2A}

c) pKi = -6.71 for D2

d) pKi = -7.95 for D4

From these values, it is clear that pipamperone has at least a 15-fold higher binding affinity for the 5-HT_{2A} and D4 receptor (of which pKi values are comparable) than for the 5-HT_{2C} and D2 receptor (of which pKi values are comparable). Hence, at any given dose, 5-HT_{2A} and D4 receptor occupancy of pipamperone will be significantly higher than 5-HT_{2C} and D2 receptor occupancy. This means that, as one decreases the dose of pipamperone, one inevitably, at some point, will arrive at a dose where clinically relevant

binding of the 5-HT_{2A} and D4 receptor still occurs but where clinically relevant binding of the 5-HT_{2C} and D2 receptor are absent.

As discussed above, the inventor surprisingly found that a daily low dose pipamperone (5-15 mg) augments the effects of SSRIs. The optimal dose of pipamperone (5-15 mg) was determined by a PK/PD (pharmacokinetics/pharmacodynamics) modeling for receptor occupancy of pipamperone for various target receptors. From this modeling, it is apparent that at the claimed low dose (5-15 mg daily) a relevant 5-HT_{2A} and D4 receptor binding still occurs, while a relevant 5-HT_{2C} and D2 receptor binding is absent. One of the aims of the present invention was exactly to minimize deleterious effects due to D2 (extrapyramidal side effects) receptor binding (occurring at over 10% receptor occupancy (RO)). Hence, lowering of the dose excludes these side effects, but maintains the beneficial effects due to 5-HT_{2A} and D4 receptor binding. As a corollary, absence of relevant D2 binding automatically indicates likewise absence of relevant 5-HT_{2C} binding, as pipamperone has similar binding affinities for both 5-HT_{2C} and D2 receptors.

In this respect, Prinssen teaches the following:

a) pipamperone has a **moderate** 5-HT_{2C} affinity (page 58, left column, 2nd paragraph),

b) pipamperone has an ED_{50} hypolocomotion effect at a dose of **22 mg/kg** (page 61, left column, last sentence, and Table 3 on page 63),

c) pipamperone has an ED_{50} hypophagia effect at a dose of **3.8 mg/kg** (page 63, right column, 2nd paragraph and Table 3),

d) pipamperone has an ED_{50} 5-HT_{2C} receptor occupancy at a dose of **14 mg/kg** (Table 3), and

e) the potency of antipsychotics to induce hypolocomotion or hypophagia are correlated with their **D2** receptor occupancy (page 64, left column, 2nd paragraph and Table 4 on page 64).

Thus, Prinssen teaches that pipamperone needs to be administered in a high dose in order to achieve a clinically relevant effect (at least 3.8 mg/kg for hypophagia, which corresponds to almost **200 mg** for a small individual of 50 kg; and at least 22 mg/kg for hypolocomotion, which corresponds to more than **1000 mg** for an individual of 50 kg). Moreover, the dose of pipamperone to induce ED_{50} 5-HT_{2C} receptor occupancy is 14 mg/kg, corresponding to **700 mg** for an individual of 50 kg). In addition, Prinssen shows that the clinical effects of antipsychotics on hypophagia and hypolocomotion are correlated with their potencies to occupy D2 receptors, illustrating an additional importance of D2 receptor occupancy. In other words, relevant 5-HT_{2C} receptor occupancy in this respect is correlated with relevant D2 receptor occupancy.

Cremers teaches that 5-HT_{2C} antagonists can be combined with SSRIs for the treatment of depression and anxiety. As Cremers indicates the importance of the 5-HT_{2C} receptor for efficient treatment, Cremers seeks to treat patients with a drug dose displaying clinically relevant 5-HT_{2C} receptor binding. As indicated above, pipamperone does not lead to a relevant 5-HT_{2C} receptor occupancy at the claimed dose, but instead requires a much higher dose to be clinically effective in respect of 5-HT_{2C} binding. Hence, pipamperone does not qualify as a drug to be combined with SSRIs according to the combined teachings of Prinssen and Cremers.

Bymaster relates to the combination of an atypical antipsychotic with a generic serotonin reuptake inhibitor (SRI) for the treatment of mood disorders. Bymaster does not teach or suggest the use of pipamperone, as is required in the present claims. Moreover, applicant maintains that pipamperone is not an "atypical" antipsychotic drug (see, e.g., "Atypical Antipsychotic Agents...," of record). In regard to dosage, Bymaster refers to dosages on page 15 et seq. Bymaster explicitly notes that "one would create a combination of the present invention by choosing a dosage of first and second component compounds according to the spirit of the above guideline" (page 16, lines 9-12). Hence,

Bymaster hints at optimizing the dosage within the given ranges. However, in contrast to the present invention, Bymaster is silent on decreasing a dose from the recommended range.

Applicant maintains that the cited references do not render the claimed invention obvious. Reconsideration and withdrawal of the rejections under 35 U.S.C. §103(a) are respectfully requested.

Status of Related Canadian Application

Patent family member Canadian Patent Application No. 2,461,248 has been allowed. A copy of the Notice of Allowance is enclose with the Supplemental Information Disclosure Statement accompanying this reply.

Status of U.S. Patent Family Members

Applicant would also like to advise the Examiner of the status of co-pending patent family members.

1. U.S. Patent Application No. 10/725,965. The claims have been subject to a restriction requirement. Office Actions on the merits of the application issued on January 23, 2008, September 15, 2008 and June 10, 2009.

2. U.S. Patent Application No. 10/803,793. The claims have been subject to a restriction requirement. Office Actions on the merits of the application issued on May 3, 2007, October 19, 2007, September 2, 2008, February 20, 2009 and November 10, 2009. Claims 50, 55, 92 and 93 are allowed.

3. U.S. Patent Application No. 10/984,683. The claims have been subject to a restriction requirement. Office Actions on the merits of the application issued on August 10, 2007, February 22, 2008, October 21, 2008, and July 21, 2009.

4. U.S. Patent Application No. 10/580,962. The claims have been subject to a

restriction requirement issued on March 6, 2009. An Office Action on the merits of the application issued on June 2, 2009.

Supplemental Information Disclosure Statement

In accordance with the duty of disclosure under 37 C.F.R. §1.56, applicant would like to direct the Examiner's attention to the references that are listed on the attached forms PTO/SB/08a. A copy of each non-US patent document is attached hereto.

CONCLUSIONS

In view of the amendments and remarks made hereinabove, reconsideration and withdrawal of the rejections set forth in the August 5, 2009 Office Action and passage of pending claims to allowance are respectfully requested. If there is any minor matter preventing the allowance of the subject application, the Examiner is requested to telephone the undersigned attorney.

The Patent Office is authorized to charge Deposit Account No. 01-1785 for following fees for a small entity: the $65.00 fee for a one month extension of time and the $180.00 fee for filing an Information Disclosure Statement. No additional fee is deemed necessary in connection with the filing of this response. However, if any other fee is required to preserve the pendency of the subject application, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 01-1785. Overpayments may also be credited to Deposit Account No. 01-1785.

Respectfully submitted,

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Dated: December 4, 2009
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